

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: MABIRE, Dominique Jean-Pierre et al.  
Serial No.: Not Assigned Art Unit: TBA  
Filed: Herewith Examiner: TBA  
For : 6-SUBSTITUTED 2-QUINOLINONES AND 2-  
QUINOXALINONES AS POLY(ADP-RIBOSE)  
POLYMERASE INHIBITORS

Mail Stop: PCT  
Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

**PRELIMINARY AMENDMENT**

Dear Sir:

Prior to examination and calculation of fees due, please amend the above-identified application as follows.

- ☒ Amendments to the Specification begin on page 2 of this paper.
- ☒ Amendments to the Claims are reflected in the listing of the claims which begins on page 3 of this paper.
- ☐ Amendments to the Drawings begin on page of this paper and include an attached replacement sheet.
- ☒ Remarks begin on page 12 of this paper.

**Specification:**

Page 1, between the Title and line 5, please insert the following new paragraph:

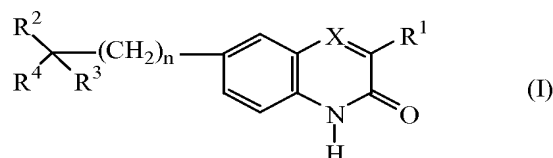
--Cross Reference to Related Applications

This application is the national stage of Application No. PCT/EP2004/013164 , filed November 18, 2004, which application claims priority from EPO Patent Application No. 03078859.0, filed December 5, 2003 --

**Listing of Claims:**

This listing of claims replaces all prior versions, and listings, of claims in the captioned application.

1. (Original) A compound of formula (I),



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

*n* is 0, 1 or 2;

*X* is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen or taken together with R<sup>1</sup> may form a bivalent radical of formula -CH=CH-CH=CH-;

R<sup>1</sup> is C<sub>1-6</sub>alkyl or thienyl;

R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>3</sup> or R<sup>4</sup> may form =O;

R<sup>3</sup> is a radical selected from

- (CH<sub>2</sub>)<sub>s</sub>- NR<sup>6</sup>R<sup>7</sup> (a-1),
- O-H (a-2),
- O-R<sup>8</sup> (a-3),
- S- R<sup>9</sup> (a-4), or
- C≡N (a-5),

wherein

*s* is 0, 1, 2 or 3;

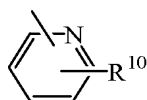
R<sup>6</sup> is -CHO, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonylaminoC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, piperidinyl, piperidinylC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkyloxy, thienylC<sub>1-6</sub>alkyl, pyrrolylC<sub>1-6</sub>alkyl, arylC<sub>1-6</sub>alkylpiperidinyl, arylcarbonylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinylC<sub>1-6</sub>alkyl, haloindozolylpiperidinylC<sub>1-6</sub>alkyl, or

arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;  
R<sup>7</sup> is hydrogen or C<sub>1-6</sub>alkyl;  
R<sup>8</sup> is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; and  
R<sup>9</sup> is di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;  
or R<sup>3</sup> is a group of formula

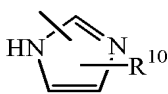


wherein

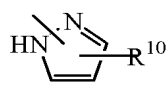
Z is a heterocyclic ring system selected from



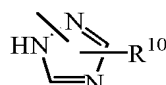
(c-1)



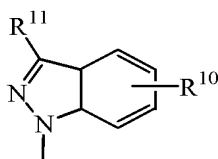
(c-2)



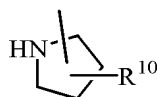
(c-3)



(c-4)

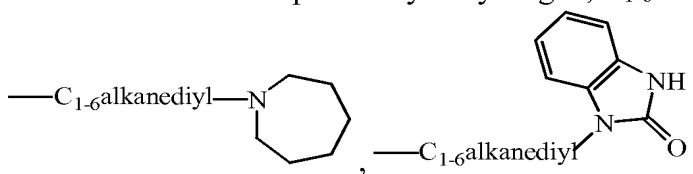


(c-5)

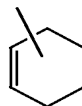


(c-6)

wherein each R<sup>10</sup> independently is hydrogen, C<sub>1-6</sub>alkyl, aminocarbonyl, hydroxy,



C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino, arylC<sub>1-6</sub>alkyl,  
di(phenylC<sub>2-6</sub>alkenyl), piperidinylC<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-6</sub>alkyl,  
aryloxy(hydroxy)C<sub>1-6</sub>alkyl, haloindazolyl, arylC<sub>1-6</sub>alkyl, arylC<sub>2-6</sub>alkenyl, morpholino,  
C<sub>1-6</sub>alkylimidazolyl, or pyridinylC<sub>1-6</sub>alkylamino;

R<sup>4</sup> is hydrogen, C<sub>1-6</sub>alkyl, furanyl, pyridinyl, arylC<sub>1-6</sub>alkyl or  ;

aryl is phenyl or phenyl substituted with halo, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxy;

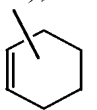
with the proviso that when

n is 0, X is N, R<sup>2</sup> is hydrogen, R<sup>3</sup> is a group of formula (b-1), Z is the heterocyclic ring system (c-2) or (c-4) wherein said heterocyclic ring system Z is attached to the rest of the molecule with a nitrogen atom, and R<sup>10</sup> is hydrogen; then

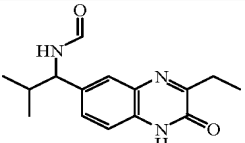
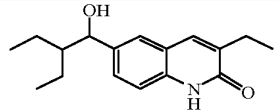
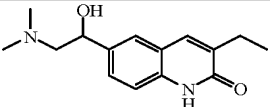
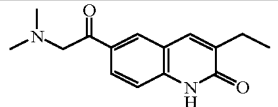
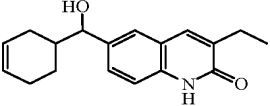
$R^4$  is other than  $C_{1-6}$ alkyl or pyridinyl.

2. (Original) A compound as claimed in claim 1 wherein  
 $n$  is 0 or 1;  $X$  is N or  $CR^5$ , wherein  $R^5$  is hydrogen;  $R^3$  is a radical selected from (a-1), (a-2) or (a-3) or is a group of formula (b-1) i.e.  $-Z-$ ;  $s$  is 0, 1 or 2;  $R^6$  is  $-CHO$ ,  $C_{1-6}$ alkyl, piperidinyl $C_{1-6}$ alkyl, arylcarbonylpiperidinyl $C_{1-6}$ alkyl or aryl $C_{1-6}$ alkyl( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl;  $R^8$  is  $C_{1-6}$ alkyl; when  $R^3$  is a group of formula (b-1) then  $Z$  is a heterocyclic ring system selected from (c-2) or (c-4); and each  $R^{10}$  independently is hydrogen,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkyloxy $C_{1-6}$ alkylamino.

3. (Currently Amended) A compound according to claim 1 ~~and 2~~ wherein  
 $n$  is 0;  $X$  is N or  $CR^5$ , wherein  $R^5$  is hydrogen;  $R^1$  is  $C_{1-6}$ alkyl;  
 $R^2$  is hydrogen or hydroxy or taken together with  $R^4$  may form  $=O$ ;  $R^3$  is a radical selected from (a-1) or (a-2);  $s$  is 0 or 1;  $R^6$  is  $-CHO$  or  $C_{1-6}$ alkyl; and  $R^4$  is

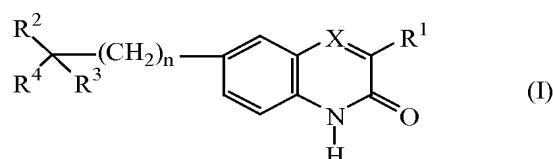
hydrogen,  $C_{1-6}$ alkyl or .

4. (Currently Amended) A compound ~~according to claim 1, 2 and 3 wherein the compound is selected from the group consisting of: compound No 1, compound No 5, compound No 7, compound No 3 and compound No 17:~~

 compound 1	 compound 5
 compound 7	 compound 3
 compound 17	

5. (Cancelled)
6. (Currently Amended) A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 ~~to 4~~.

7. (Cancelled).
8. (Currently Amended) ~~A method of treating~~ Use of a compound for the manufacture of a medicament for the treatment in a subject of a PARP mediated disorder, comprising administering to the subject a therapeutically effective amount of ~~wherein said compound is a compound of formula (I)~~



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

*n* is 0, 1 or 2;

*X* is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen or taken together with R<sup>1</sup> may form a bivalent radical of formula -CH=CH-CH=CH-;

R<sup>1</sup> is C<sub>1-6</sub>alkyl or thienyl;

R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>3</sup> or R<sup>4</sup> may form =O;

R<sup>3</sup> is a radical selected from

- (CH<sub>2</sub>)<sub>s</sub>- NR<sup>6</sup>R<sup>7</sup> (a-1),
- O-H (a-2),
- O-R<sup>8</sup> (a-3),
- S- R<sup>9</sup> (a-4), or
- C≡N (a-5),

wherein

*s* is 0, 1, 2 or 3;

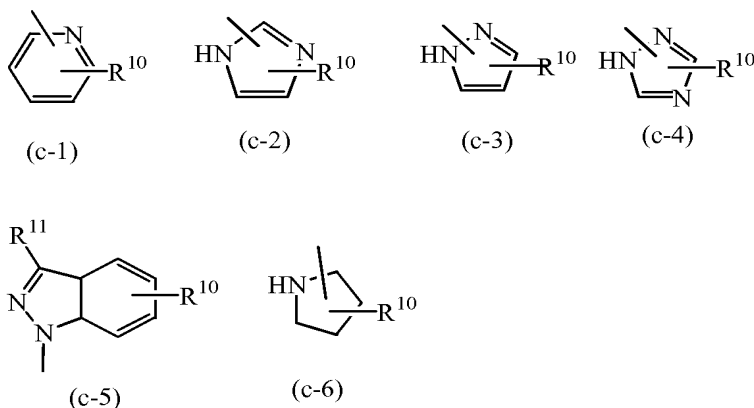
R<sup>6</sup> is -CHO, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl, di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonylaminoC<sub>1-6</sub>alkyl, piperidinyC<sub>1-6</sub>alkylaminocarbonyl, piperidiny, piperidinyC<sub>1-6</sub>alkyl, piperidinyC<sub>1-6</sub>alkylaminocarbonyl, C<sub>1-6</sub>alkyloxy, thienylC<sub>1-6</sub>alkyl, pyrrolylC<sub>1-6</sub>alkyl, arylC<sub>1-6</sub>alkylpiperidiny, arylcarbonylC<sub>1-6</sub>alkyl, arylcarbonylpiperidinyC<sub>1-6</sub>alkyl, haloindozolylpiperidinyC<sub>1-6</sub>alkyl, or

arylC<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;  
R<sup>7</sup> is hydrogen or C<sub>1-6</sub>alkyl;  
R<sup>8</sup> is C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylcarbonyl or di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl; and  
R<sup>9</sup> is di(C<sub>1-6</sub>alkyl)aminoC<sub>1-6</sub>alkyl;  
or R<sup>3</sup> is a group of formula

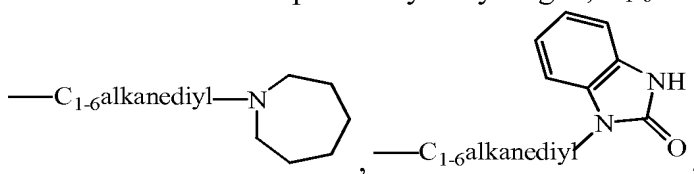


wherein

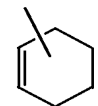
Z is a heterocyclic ring system selected from



wherein each R<sup>10</sup> independently is hydrogen, C<sub>1-6</sub>alkyl, aminocarbonyl, hydroxy,



C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylamino, arylC<sub>1-6</sub>alkyl,  
di(phenylC<sub>2-6</sub>alkenyl), piperidinylC<sub>1-6</sub>alkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-10</sub>cycloalkylC<sub>1-6</sub>alkyl,  
aryloxy(hydroxy)C<sub>1-6</sub>alkyl, haloindazolyl, arylC<sub>1-6</sub>alkyl, arylC<sub>2-6</sub>alkenyl, morpholino,  
C<sub>1-6</sub>alkylimidazolyl, or pyridinylC<sub>1-6</sub>alkylamino;

R<sup>4</sup> is hydrogen, C<sub>1-6</sub>alkyl, furanyl, pyridinyl, arylC<sub>1-6</sub>alkyl or  ;

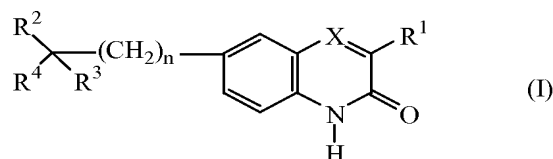
aryl is phenyl or phenyl substituted with halo, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxy.

9. (Cancelled)

10. (Currently Amended) A method for enhancing the effectiveness of chemotherapy of comprising administration of a compound according to claim 1, in a therapeutically

effective amount so as to increase sensitivity of cells to chemotherapy, prior to administration of said chemotherapy ~~Use according to claim 8 and 9 wherein the treatment involves chemosensitization.~~

11. (Currently Amended) A method for enhancing the effectiveness of radiotherapy of comprising administration of a compound according to claim 1, in a therapeutically effective amount so as to increase sensitivity of cells to ionizing radiation, prior to administration of said radiotherapy ~~Use according to claim 8 and 9 wherein the treatment involves radiosensitization.~~
12. (Original) A combination of a compound with a chemotherapeutic agent wherein said compound is a compound of formula (I)



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

*n* is 0, 1 or 2;

*X* is N or CR<sup>5</sup>, wherein R<sup>5</sup> is hydrogen or taken together with R<sup>1</sup> may form a bivalent radical of formula -CH=CH-CH=CH-;

R<sup>1</sup> is C<sub>1-6</sub>alkyl or thienyl;

R<sup>2</sup> is hydrogen or hydroxy or taken together with R<sup>3</sup> or R<sup>4</sup> may form =O;

R<sup>3</sup> is a radical selected from

- (CH<sub>2</sub>)<sub>8</sub>- NR<sup>6</sup>R<sup>7</sup> (a-1),
- O-H (a-2),
- O-R<sup>8</sup> (a-3),
- S- R<sup>9</sup> (a-4), or
- C≡N (a-5),

wherein



s is 0, 1, 2 or 3;

$R^6$  is  $-CHO$ ,  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonyl, di( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonylamino $C_{1-6}$ alkyl, piperidiny $C_{1-6}$ alkylaminocarbonyl, piperidiny $C_{1-6}$ alkyl, piperidiny $C_{1-6}$ alkylaminocarbonyl,  $C_{1-6}$ alkyloxy, thienyl $C_{1-6}$ alkyl, pyrrolyl $C_{1-6}$ alkyl, aryl $C_{1-6}$ alkylpiperidiny $C_{1-6}$ alkyl, arylcarbonyl $C_{1-6}$ alkyl, arylcarbonylpiperidiny $C_{1-6}$ alkyl, haloindozolylpiperidiny $C_{1-6}$ alkyl, or aryl $C_{1-6}$ alkyl( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl;

$R^7$  is hydrogen or  $C_{1-6}$ alkyl;

$R^8$  is  $C_{1-6}$ alkyl,  $C_{1-6}$ alkylcarbonyl or di( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl; and

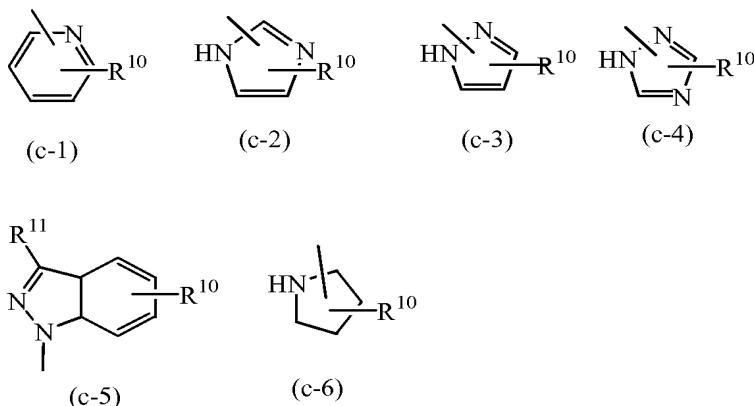
$R^9$  is di( $C_{1-6}$ alkyl)amino $C_{1-6}$ alkyl;

or  $R^3$  is a group of formula

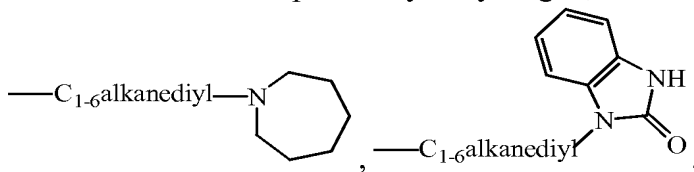


wherein

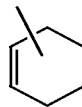
Z is a heterocyclic ring system selected from



wherein each  $R^{10}$  independently is hydrogen,  $C_{1-6}$ alkyl, aminocarbonyl, hydroxy,



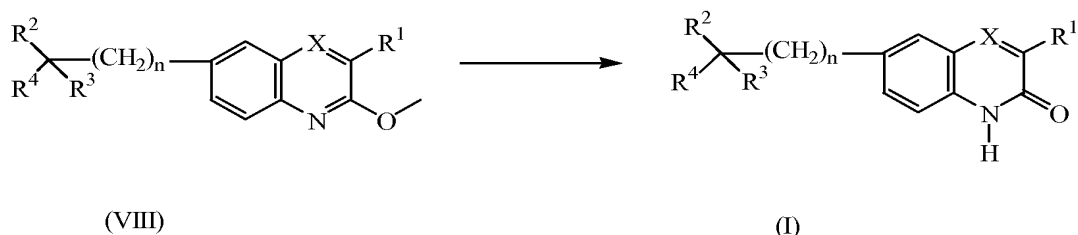
$C_{1-6}$ alkyloxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy $C_{1-6}$ alkylamino, aryl $C_{1-6}$ alkyl, di(phenyl $C_{2-6}$ alkenyl), piperidiny $C_{1-6}$ alkyl,  $C_{3-10}$ cycloalkyl,  $C_{3-10}$ cycloalkyl $C_{1-6}$ alkyl, aryloxy(hydroxy) $C_{1-6}$ alkyl, haloindazolyl, aryl $C_{1-6}$ alkyl, aryl $C_{2-6}$ alkenyl, morpholino,  $C_{1-6}$ alkylimidazolyl, or pyridiny $C_{1-6}$ alkylamino;

$R^4$  is hydrogen,  $C_{1-6}$ alkyl, furanyl, pyridiny $C_{1-6}$ alkyl or  ;

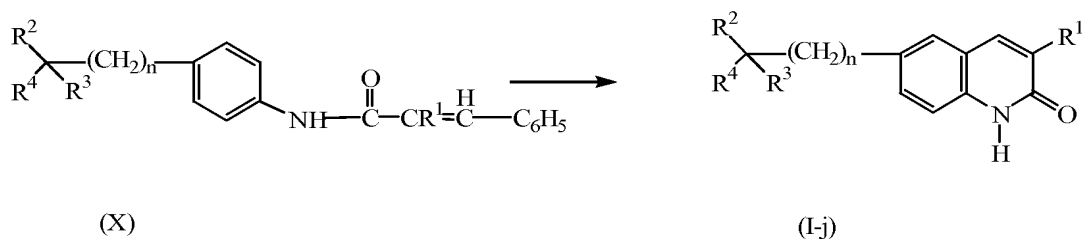
aryl is phenyl or phenyl substituted with halo, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyloxy.

13. (Currently Amended) A process for preparing a compound as claimed in claim 1, comprising: ~~characterized by~~

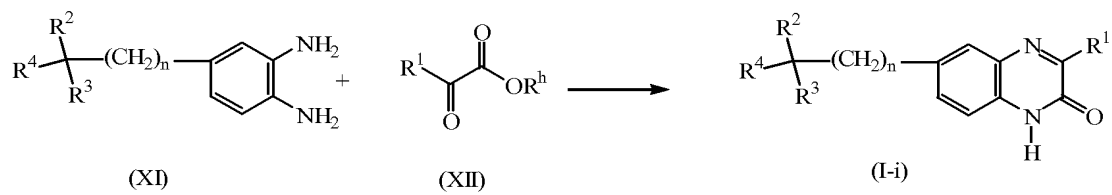
a) ~~the hydrolysis of intermediates of formula (VIII), according to art known methods, by submitting the intermediates of formula (VIII) to appropriate reagents, such as, tin chloride, acetic acid and hydrochloric acid, in the presence of a reaction inert solvent, e.g. tetrahydrofuran.~~



b) ~~the cyclization of intermediates of formula (X), according to art known cyclizing procedures into compounds of formula (I) wherein X is CH herein referred to as compounds of formula (I-j), preferably in the presence of a suitable Lewis Acid, e.g. aluminum chloride either neat or in a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, chlorobenzene, methylbenzene and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane and the like; an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like or mixtures of such solvents.~~



c) ~~the condensation of an appropriate ortho-benzenediamine of formula (XI) with an ester of formula (XII) wherein R<sup>h</sup> is C<sub>1-6</sub>alkyl, into compounds of formula (I), wherein X is N, herein referred to as compounds of formula (I-i), in the presence of a carboxylic acid, e.g. acetic acid and the like, a mineral acid such as, for example hydrochloric acid, sulfuric acid, or a sulfonic acid such as, for example, methane-sulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid and the like.~~



**REMARKS**

Consideration of the captioned application in view of the foregoing amendments and following remarks is requested.

The specification has been amended to refer to the priority applications.

Claims 1-4, 6, 8 and 10-13 are currently pending. Claims 3, 4, 6, 8, 10, 11 and 13 are currently amended, without disclaimer of, or prejudice to, the subject matter deleted, to remove multiple dependencies and to comport with U.S. style claim practice. Claims 5, 7 and 9 are hereby cancelled, without disclaimer of, or prejudice to, the subject matter thereof. No new matter has been added.

Accordingly, the claims pending and under consideration are claims 1-4, 6, 8 and 10-13.

Early favourable action on the merits is respectfully requested.

Applicant respectfully requests that a timely Notice of Allowance of claims 1-4, 6, 8 and 10-13 be issued in this case.

Respectfully submitted,

/Alana G. Kriegsman/

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Dated: May 30, 2006